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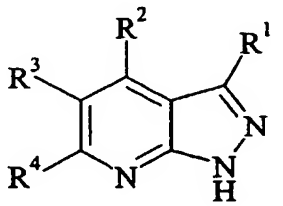
(54) Title: PYRAZOLOPYRIDINE DERIVATIVES



(I)

(57) Abstract: Compounds of formula (I), or a salt thereof, or a solvate thereof, wherein, R^1 is halo, -N=N-heteroaryl, $-CO_2R^5$, $-NHCH_2R^6$; or $-CONR^7R^8$; R^2 is H or aryl; R^3 is H or aryl, wherein the aryl ring may be optionally substituted by one or more substituents, which may be the same or different, selected from halo; R^4 is H; R^5 is alkyl; and R^6 is H, alkyl, cycloalkyl, aryl or aralkyl; R^7 and R^8 are selected from H and alkyl; and with the proviso that when R^1 is halo, at least one of R^2 and/or R^3 is aryl; a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds and composition in medicine.

PYRAZOLOPYRIDINE DERIVATIVES

This invention relates to novel compounds, in particular to novel pyrazolopyridine derivatives, to processes for the preparation of such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds in medicine.

GSK-3 is a serine/threonine protein kinase composed of two isoforms (α and β) which are encoded by distinct genes. GSK-3 is one of several protein kinases which phosphorylates glycogen synthase (GS) (Embi *et al., Eur. J. Biochem.*, **(107)**, 519-527, (1980)). The α and β isoforms have a monomeric structure and are both found in mammalian cells. Both isoforms phosphorylate muscle glycogen synthase (Cross *et al., Biochemical Journal*, **(303)**, 21-26, (1994)) and these two isoforms show good homology between species (*e.g.* human and rabbit GSK-3α are 96% identical).

Type II diabetes (or Non-Insulin Dependent Diabetes Mellitus, NIDDM) is a multifactorial disease. Hyperglycaemia is due to insulin resistance in the liver, muscle and other tissues coupled with inadequate or defective secretion of insulin from pancreatic islets. Skeletal muscle is the major site for insulin-stimulated glucose uptake and in this tissue, glucose removed from the circulation is either metabolised through glycolysis and the TCA cycle, or stored as glycogen. Muscle glycogen deposition plays the more important role in glucose homeostasis and Type II diabetic subjects have defective muscle glycogen storage.

The stimulation of glycogen synthesis by insulin in skeletal muscle results from the dephosphorylation and activation of glycogen synthase (Villar-Palasi C. and Larner J., *Biochim. Biophys. Acta.*, **(39)**, 171-173, (1960), Parker P.J. *et al., Eur. J. Biochem.*, **(130)**, 227-234, (1983) and Cohen P., *Biochem. Soc. Trans.*, **(21)**, 555-567, (1993)). The phosphorylation and dephosphorylation of GS are mediated by specific kinases and phosphatases. GSK-3 is responsible for phosphorylation and deactivation of GS, while glycogen bound protein phosphatase 1 (PP1G) dephosphorylates and activates GS. Insulin both inactivates GSK-3 and activates PP1G (Srivastava A.K. and Pandey S.K., *Mol. and Cellular Biochem.*, **(182)**, 135-141, (1998)).

Chen *et al.* (*Diabetes*, **(43)**, 1234-1241, (1994)) found that there was no difference in the mRNA abundance of PP1G between patients with Type II diabetes and control patients, suggesting that an increase in GSK-3 activity might be important in Type II

diabetes. It has also recently been demonstrated that GSK-3 is overexpressed in Type II diabetic muscle and that an inverse correlation exists between skeletal muscle GSK-3α activity and insulin action (Nikoulina *et al.*, *Diabetes*, **(49)**, 263-271, (2000)). Overexpression of GSK-3β and constitutively active GSK-3β(S9A, S9E) mutants in HEK-293 cells resulted in suppression of glycogen synthase activity (Eldar-Finkelman *et al.*, *PNAS*, **(93)**, 10228-10233, (1996)) and overexpression of GSK-3β in CHO cells, expressing both insulin receptor and insulin receptor substrate 1 (IRS-1), resulted in an impairment of insulin action (Eldar-Finkelman and Krebs, *PNAS*, **(94)**, 9660-9664, (1997)). Recent evidence for the involvement of elevated GSK-3 activity and the development of insulin resistance and type II diabetes in adipose tissue has emerged from studies undertaken in diabetes and obesity prone C57BL/6J mice (Eldar-Finkelman *et al.*, *Diabetes*, **(48)**, 1662-1666, (1999)).

GSK-3 has been shown to phosphorylate other proteins *in vitro* including the eukaryotic initiation factor eIF-2B at $Serine^{540}$ (Welsh *et al.*, *FEBS Letts.*, **(421)**, 125-130, (1998)). This phosphorylation results in an inhibition of eIF-2B activity and leads to a reduction in this key regulatory step of translation. In disease states, such as diabetes, where there is elevated GSK-3 activity this could result in a reduction of translation and potentially contribute to the pathology of the disease.

Several aspects of GSK-3 functions and regulation in addition to modulation of glycogen synthase activity indicate that inhibitors of this enzyme may be effective in treatment of disorders of the central nervous system. GSK-3 activity is subject to inhibitory phosphorylation by PI 3 kinase-mediated or Wnt-1 class-mediated signals that can be mimicked by treatment with lithium, a low mM inhibitor of GSK-3 (Stambolic V., Ruel L. and Woodgett J.R., *Curr. Biol.*, **(6)**, 1664-8, (1996)).

GSK-3 inhibitors may be of value as neuroprotectants in treatment of acute stroke and other neurotraumatic injuries. Roles for PI 3-kinase signalling through PKB/akt to promote neuronal cell survival are well established, and GSK-3 is one of a number of PKB/akt substrates to be identified that can contribute to the inhibition of apoptosis via this pathway (Pap and Cooper, *J. Biol. Chem.*, **(273)**, 19929-19932, ((1998)). Evidence suggests that astrocytic glycogen can provide an alternative energy source to facilitate neuronal survival under conditions of glucose deprivation (for example, see Ransom B.R. and Fern R., *Glia*, **(21)**, 134-141, (1997) and references therein). Lithium is known to

protect cerebellar granule neurons from death (D'Mello *et al.*, *Exp. Cell Res.*, **(211)**, 332-338, (1994) and Volonte *et al.*, *Neurosci. Letts.*, **(172)**, 6-10, (1994)) and chronic lithium treatment has demonstrable efficacy in the middle cerebral artery occlusion model of stroke in rodents (Nonaka and Chuang, *Neuroreport*, **(9)**, 2081-2084, (1998)). Wnt-induced axonal spreading and branching in neuronal culture models has been shown to correlate with GSK-3 inhibition (Lucas and Salinas, *Dev. Biol.*, **(192)**, 31-44, (1997)) suggesting additional value of GSK-3 inhibitors in promoting neuronal regeneration following neurotraumatic insult.

Tau and β-catenin, two known *in vivo* substrates of GSK-3, are of direct relevance in consideration of further aspects of the value of GSK-3 inhibitors in relation to treatment of chronic neurodegenerative conditions. Tau hyperphosphorylation is an early event in neurodegenerative conditions such as Alzheimer's disease (AD), and is postulated to promote microtubule disassembly. Lithium has been reported to reduce the phosphorylation of tau, enhance the binding of tau to microtubules, and promote microtubule assembly through direct and reversible inhibition of glycogen synthase kinase-3 (Hong M., Chen D.C., Klein P.S. and Lee V.M., *J. Biol. Chem.*, **(272)**, 25326-32, (1997). β-catenin is phosphorylated by GSK-3 as part of a tripartite complex with axin, resulting in β-catenin being targetted for degradation (Ikeda *et al.*, *J. EMBO.*, **(17)**, 1371-1384, (1998)). Inhibition of GSK-3 activity is a key mechanism by which cytosolic levels of catenin are stabilised and hence promote β-catenin-LEF-1/TCF transcriptional activity (Eastman, Grosschedl, *Curr. Opin. Cell. Biol.*, **(11)**, 233, (1999)). Rapid onset AD mutations in presenilin-1 (PS-1) have been shown to decrease the cytosolic β-catenin pool in transgenic mice. Further evidence suggests that such a reduction in available β-catenin may increase neuronal sensitivity to amyloid mediated death through inhibition of β-catenin-LEF-1/TCF transcriptional regulation of neuroprotective genes (Zhang *et al.*, *Nature*, **(395)**, 698-702, (1998)). A likely mechanism is suggested by the finding that mutant PS-1 protein confers decreased inactivation of GSK-3 compared with normal PS-1 (Weihl C.C., Ghadge G.D., Kennedy S.G., Hay N., Miller R.J. and Roos R.P., *J. Neurosci.*, **(19)**, 5360-5369, (1999)).

International Patent Application Publication Number WO 97/41854 (University of Pennsylvania) discloses that an effective drug for the treatment of manic depression is lithium, but that there are serious drawbacks associated with this treatment. Whilst the

precise mechanism of action of this drug for treatment of manic depression remains to be fully defined, current models suggest that inhibition of GSK-3 is a relevant target that contributes to the modulation of AP-1 DNA binding activity observed with this compound (see Manji *et al.*, *J. Clin. Psychiatry*, **(60)** (suppl 2), 27-39, (1999) for review).

GSK-3 inhibitors may also be of value in treatment of schizophrenia. Reduced levels of β-catenin have been reported in schizophrenic patients (Cotter D., Kerwin R., al-Sarraji S., Brion J.P., Chadwich A., Lovestone S., Anderton B., and Everall I., *Neuroreport*, **(9)**, 1379-1383, (1998)) and defects in pre-pulse inhibition to startle response have been observed in schizophrenic patients (Swerdlow *et al.*, *Arch. Gen. Psychiat.*, **(51)**, 139-154, (1994)). Mice lacking the adaptor protein dishevelled-1, an essential mediator of Wnt-induced inhibition of GSK-3, exhibit both a behavioural disorder and defects in pre-pulse inhibition to startle response (Lijam N., Paylor R., McDonald M.P., Crawley J.N., Deng C.X., Herrup K., Stevens K.E., Maccaferri G., McBain C.J., Sussman D.J., and Wynshaw-Boris A., *Cell*, **(90)**, 895-905, (1997)). Together, these findings implicate deregulation of GSK-3 activity as contributing to schizophrenia. Hence, small molecule inhibitors of GSK-3 catalytic activity may be effective in treatment of this mood disorder.

The finding that transient β-catenin stabilisation may play a role in hair development (Gat *et al.*, *Cell*, **(95)**, 605-614, (1998)) suggests that GSK-3 inhibitors could be used in the treatment of baldness.

Studies on fibroblasts from the GSK-3β knockout mouse (Hoeflich K.P. *et al.*, *Nature*, **(406)**, 86-90, (2000)) support a role for this kinase in positively regulating the activity of NFkB. This transcription factor mediates cellular responses to a number of inflammatory stimuli. Therefore, pharmacologic inhibition of GSK-3 may be of use in treating inflammatory disorders through the negative regulation of NFkB activity.

The compounds of the present invention are pyrazolopyridine derivatives. Other pyrazolopyridine derivatives have been described previously for use in alternative medicinal applications. For example, International Patent Application Publication Numbers WO 97/23480 and WO 98/43962 describe various fused heterocyclic compounds, which may include pyrazolopyridazines, which are useful as antagonists of the $\alpha_V\beta_3$-integrin and related cell surface adhesive protein receptors. Such compounds are indicated to be useful in the treatment of conditions such as angiogenic disorders,

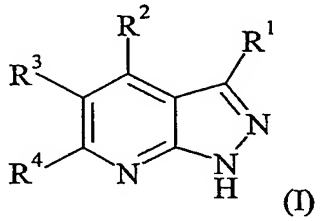
inflammation, bone degradation, cancer metastasis, diabetic retinopathy, thrombosis, restenosis, macular degeneration, and other conditions mediated by cell adhesion and/or cell migration and/or angiogenesis.

International Patent Application Publication Number WO 00/26211 describes various fused heterocyclic compounds, which may include pyrazolopyridines, which are useful in inhibiting thrombin and associated thrombotic occlusions. Such compounds are indicated to be useful in the treatment of conditions such as angina, myocardial infarction, thrombotic stroke, embolic stroke and the like.

International Patent Application Publication Number WO 02/24694 describes a variety of pyrazolopyridine and pyrazolopyridazine derivatives having activity as inhibitors of GSK-3.

We have now discovered that a series of pyrazolo[3,4-b]pyridines are potent and selective inhibitors of GSK-3. These compounds are indicated to be useful for the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

Accordingly, in a first aspect, the present invention provides a compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is halo, -N=N-heteroaryl, $-CO_2R^5$, $-NHCH_2R^6$; or $-CONR^7R^8$;

R^2 is H or aryl;

R^3 is H or aryl, wherein the aryl ring may be optionally substituted by one or more substituents, which may be the same or different, selected from halo;

R^4 is H;

R^5 is alkyl;

R^6 is H, alkyl, cycloalkyl, aryl or aralkyl; and

R^7 and R^8 are selected from H and alkyl;

with the proviso that when R^1 is halo, at least one of R^2 and/or R^3 is aryl (hereafter "the compounds of the invention").

Suitably, R^1 is halo, -N=N-heteroaryl or $-CO_2R^5$. Preferably, R^1 is chloro, bromo, -N=N-2-pyrrolyl or $-CO_2Et$.

Suitably, R^2 is H or phenyl. Preferably, R^2 is H.

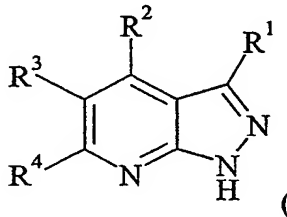
Suitably, R^3 is H, phenyl or fluorophenyl. Preferably, R^3 is H, phenyl or 3-fluorophenyl.

Suitably, R^6 is alkyl or aryl.

Suitably, R^7 is H.

Suitably, R^8 is alkyl.

There is also provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is bromo, chloro, -N=N-2-pyrrolyl, $-CO_2Et$, $-NHCH_2Ph$, –NHEt or $-CONHBu^n$;

R^2 is H or phenyl;

R^3 is H, phenyl or 3-fluorophenyl; and

R^4 is H,

with the proviso that when R^1 is bromo or chloro, either R^2 is phenyl and/or R^3 is phenyl or 3-fluorophenyl.

Preferred compounds of formula (I) which are of special interest as agents useful in the treatment and/or prophylaxis of conditions associated with a need for inhibition of GSK-3 are provided in Table 1 below.

Certain compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the isomeric forms of the compounds of formula (I) whether as individual isomers or as mixtures of isomers, including geometric isomers and racemic modifications.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing 2 to 12 carbon atoms, suitably 2 to 6 carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof. Such alkenyl groups in particular include ethenyl, propenyl, butenyl, pentenyl and hexenyl. Where appropriate, such alkenyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the term "alkynyl" refers to hydrocarbon groups of either straight or branched configuration with one or more carbon-carbon triple bonds which may occur at any stable point in the chain, containing 3 to 12 carbon atoms, suitably 3 to 6 carbon atoms. Such alkynyl groups in particular include propynyl, butynyl and pentynyl. Where

appropriate, such alkynyl groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical. Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl, biphenyl and naphthyl, particularly phenyl. Such aryl groups may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, -NO_2, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy and di-C_{1-6} alkylamino.

As used herein, the term "heteroaryl" as a group or part of a group refers to stable heterocyclic aromatic single and fused rings containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur. A fused heteroaryl ring system may include carbocyclic rings and need include only one heteroaryl ring. Such heteroaryl groups include furyl, thienyl, pyridazinyl, pyridyl, quinolinyl, indolyl, benzoxazolyl, and benzothiazolyl. Each ring may be optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, -NO_2, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

As used herein the terms "halo" include iodo, bromo, chloro or fluoro, suitably bromo, chloro and fluoro, especially bromo and chloro.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, *inter alia*, having a pharmaceutically acceptable level of purity excluding

normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.

One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Suitable salts are pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Suitable pharmaceutically acceptable salts include salts of acidic moieties of the compounds of formula (I) when they are present, for example salts of carboxy groups or phenolic hydroxy groups.

Suitable salts of acidic moieties include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable solvates are pharmaceutically acceptable solvates.

Suitable pharmaceutically acceptable solvates include hydrates.

For the avoidance of doubt when used herein the term "diabetes" includes diabetes mellitus, especially Type 2 diabetes, and conditions associated with diabetes mellitus.

The term "conditions associated with diabetes" includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

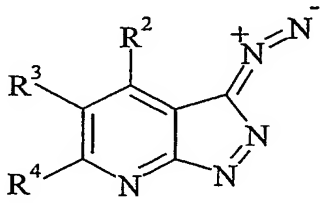
The term "conditions associated with the pre-diabetic state" includes conditions such as insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

The term "conditions associated with diabetes mellitus itself" includes hyperglycaemia, insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance.

The term "complications associated with diabetes mellitus" includes renal disease, especially renal disease associated with Type II diabetes, neuropathy and retinopathy. Renal diseases associated with Type II diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

The term "neurotraumatic diseases" includes both open or penetrating head trauma, such as caused by surgery, or a closed head trauma injury, such as caused by an injury to the head region, ischaemic stroke including acute stroke, particularly to the brain area, transient ischaemic attacks following coronary by-pass and cognitive decline following other transient ischaemic conditions.

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is halo and wherein R^2, R^3 and R^4 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I), with a compound of formula (III),

H—X

(III)

wherein X is halo, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compounds of formulae (II) and (III) is carried out optionally in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Where employed, suitable solvents include water. Suitable reaction temperatures include those in the range of 10°C to 150°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 0.5 to 24 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the residue neutralised using a suitable base, such as saturated sodium bicarbonate solution, and the products isolated by filtration. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, compound (III) is added dropwise, with stirring, to a solution of the compound of formula (II) in water. The mixture is heated to 100 to 130 °C, preferably 120 °C, for 20 to 40 minutes, preferably 30 minutes. The resulting mixture is then cooled to room temperature, diluted with water, and neutralised by the addition of a suitable aqueous base, such as saturated sodium bicarbonate solution, with stirring. The resulting solid is then collected by filtration, washed with a suitable solvent, such as water, and dried *in vacuo* to afford the desired compound of formula (I).

In a further preferred aspect, compound (III) is added dropwise, with stirring, to a solution of the compound of formula (II) in water. The mixture is stirred at ambient temperature for 12-24 hours, preferably 12 hours. The resulting mixture is then neutralised by the addition of a suitable aqueous base, such as saturated sodium bicarbonate solution, with stirring. The resulting solid is then collected by filtration, washed with a suitable solvent, such as water, and dried *in vacuo* to afford the desired compound of formula (I).

It will be appreciated that compounds of formula (I) where R^1 is halo can also be prepared directly by methods known in the art (e.g. *J. March, Advanced Organic Chemistry, 4th Edition, 1992, Wiley Interscience*).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is –N=N-heteroaryl and wherein R^2, R^3 and R^4 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),

wherein R^2, R^3 and R^4 are as defined in relation to formula (I), with a compound of formula (IV),

Ar—H

(IV)

wherein Ar is heteroaryl, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

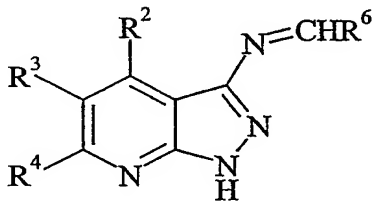
(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compounds of formulae (II) and (IV) is carried out optionally in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitably the reaction is performed in the absence of a solvent. Suitable reaction temperatures include those in the range of 10°C to 30°C. Suitable reaction times are those in the range 12-72 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation,

chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the compound of formula (II) is added dropwise, with stirring, to the compound of formula (IV) at ambient temperature and is left to stir for 12-72 hours, preferably 48 hours. The resulting solid is then collected by filtration, washed with a suitable solvent, such as dichloromethane, and dried *in vacuo* to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is $-NHCH_2R^6$, and wherein R^2, R^3, R^4 and R^6 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

wherein R^2, R^3, R^4 and R^6 are as defined in relation to formula (I), with a reducing agent, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

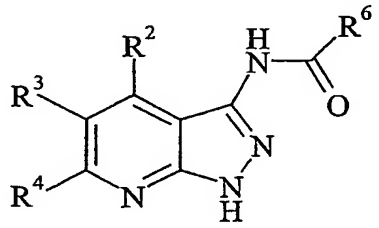
(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compound of formula (V) and a reducing agent is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable reducing agents include sodium triacetoxyborohydride, sodium cyanoborohydride, resin supported cyanoborohydride and sodium borohydride. It will be appreciated that certain reducing agents, such as sodium triacetoxyborohydride or sodium borohydride, may optionally be used in combination with a suitable carboxylic acid, such

as glacial acetic acid. Suitable solvents include 1,2-dimethoxyethane, tetrahydrofuran and 1,4-dioxan. Suitable reaction temperatures include those in the range of 10°C to 60°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12-72 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a suspension of the compound of formula (V), sodium triacetoxyborohydride and glacial acetic acid in tetrahydrofuran are stirred at ambient temperature for 12-72 hours, preferably 48 hours. The resulting solution is then treated with a suitable aqueous base, such as saturated bicarbonate solution, and the mixture extracted with a suitable solvent, such as ethyl acetate. The organic phases are then combined, dried with a suitable drying agent, such as anhydrous magnesium sulphate, and evaporated. The resulting residue is typically purified by chromatography on silica gel using a suitable solvent or mixture of solvents, such as a gradient of dichloromethane – 10% acetone/dichloromethane, to afford the desired compound of formula (I).

It will be appreciated that compounds of formula (I) where R^1 is $-NHCH_2R^6$, and wherein R^2, R^3, R^4 and R^6 are as hereinbefore defined or a salt thereof and/or a solvate thereof, may also be prepared by reacting a compound of formula (VI),



(VI)

wherein R^2, R^3, R^4 and R^6 are as defined in relation to formula (I), with a reducing agent, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

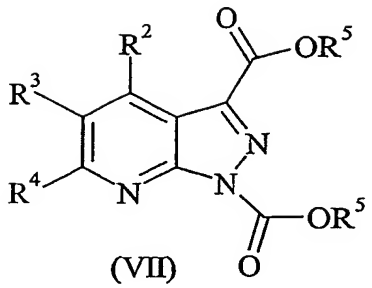
(iii) preparing an appropriate derivative of the compound so formed,

thereby constituting a further aspect of the present invention.

The reaction between the compound of formula (VI) and a reducing agent is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable reducing agents include lithium aluminium hydride and diborane. Suitable solvents include 1,4-dioxan, tetrahydrofuran and 1,2-dimethoxyethane. Suitable reaction temperatures include those in the range of 20°C to 120°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-6 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, lithium aluminum hydride, suitably as a solution in a suitable solvent such as tetrahydrofuran, is added to a stirred solution of the compound of formula (VI) in 1,4-dioxan. The reaction mixture is heated to reflux and allowed to stir for a further 1 to 6 hours, preferably 2 hours, after which the mixture is allowed to cool. When present, any excess of lithium aluminium hydride is decomposed by the addition of a suitable quantity of water. The reaction mixture is then concentrated (by evaporation), and typically purified by column chromatography with a suitable solvent or mixture of solvents, such as 2% v/v methanol in dichloromethane, to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is $-CO_2R^5$, and wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (VII),



(VII)

wherein R^2, R^3, R^4 and R^5 are as defined in relation to formula (I), with a nucleophile, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

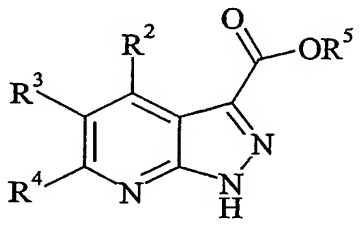
(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compound of formula (VII) and a nucleophile is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable nucleophiles include primary amines, such as benzylamine, and secondary amines, such as piperidine. Suitable solvents include ethanol and tetrahydrofuran. Suitable reaction temperatures include those in the range of 20°C to 100°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12-48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the nucleophile, such as benzylamine, is added to a stirred solution of the compound of formula (VII) in ethanol. The reaction mixture is heated to reflux and left to stir, under reflux, for a further 12 to 48 hours, preferably 12 hours. The resulting reaction mixture is allowed to cool, the solvent evaporated, and the residue is typically purified by chromatography on silica gel using a suitable solvent or mixture of solvents, such as dichloromethane/ether, to afford the desired compound of formula (I).

According to a further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) where R^1 is -$CONR^7R^8$, and wherein R^2, R^3, R^4, R^7 and R^8 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (I) where R^1 is – CO_2R^5,



(I)

wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined, with an amine, NHR^7R^8, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

The reaction between the compound of formula (I) and an amine, NHR^7R^8 is carried out optionally in the presence of a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable amines include primary amines, such as n-butylamine. Suitably, the reaction is performed in the absence of a solvent. Suitable reaction temperatures include those in the range of 20°C to 150°C and, as appropriate, the reflux temperature of the solvent or the amine, NHR^7R^8. Suitable reaction times are those in the range 6-24 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, a mixture of the compound of formula (I) where R^1 is $-CO_2R^5$ and the amine, NHR^7R^8 is heated at reflux, with stirring, for 6 to 24 hours, preferably 12 hours. The resulting solution is evaporated to dryness, and typically the residue is triturated with a suitable solvent, such as ether, to afford the desired compound of formula (I) where R^1 is $-CONR^7R^8$.

The above-mentioned conversions of a compound of formula (I) into another compound of formula (I) includes any conversion which may be effected using conventional procedures, but in particular the said conversions include any combination of:

(i) converting one group R^1 into another group R^1;

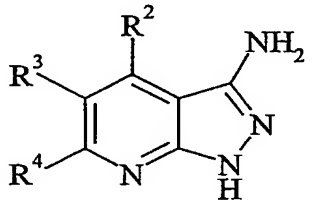
(ii) converting one group R^2 into another group R^2;

(iii) converting one group R^3 into another group R^3.

The above-mentioned conversions (i) and (ii) may be carried out using any appropriate method under conditions determined by the particular groups chosen.

The above-mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Compounds of formula (II) may be prepared by reaction of a compound of formula (VIII),



(VIII)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I), with an acid and an aqueous metal nitrite, followed by basification.

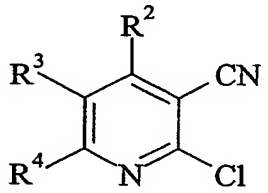
The reaction between the compound of formula (VIII) with an acid and an aqueous metal nitrite is carried out under standard diazotisation conditions. The reaction is carried out in a suitable solvent, under conventional conditions, at a suitable temperature, providing a suitable rate of formation of the required product, over a

suitable reaction time. A suitable acid is sulphuric acid. Suitable aqueous metal nitrites include aqueous potassium or sodium nitrite. Suitable bases include potassium or sodium carbonate. A suitable solvent is water. Suitable reaction temperatures include those in the range of -20°C to 5°C. Suitable reaction times are those in the range 0.5-4 hours. The reaction products are isolated using conventional methods. Conventional methods of cooling may be employed, for example ice/salt baths. The reaction products are typically purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the acid is added dropwise to a stirred suspension of the compound of formula (VIII) in water with cooling (salt/ice bath). The aqueous metal nitrite is then added dropwise to the resulting reaction mixture, keeping the reaction temperature from -20 to 5 °C, preferably at or about 0°C. Upon addition of the aqueous metal nitrite, the reaction mixture is allowed to stir for a further 15 minutes to 1 hour, preferably 30 minutes. The resulting mixture is basified with a suitable base, such as sodium carbonate, and the resulting solid is collected by filtration, washed with a suitable solvent, such as water, and dried at room temperature under high vacuum to afford the desired compound of formula (II).

Compounds of formula (II) wherein at least one of R^2 and/or R^3 is aryl are believed to be novel, and accordingly form a further aspect of the present invention.

Compounds of formula (VIII) may be prepared by reaction of a compound of formula (IX),



(IX)

wherein,

R^2, R^3 and R^4 are as defined in relation to formula (I), with hydrazine or a hydrate thereof.

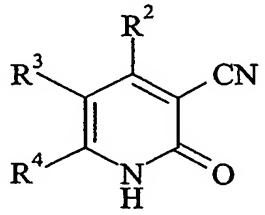
The reaction between the compound of formula (IX) and hydrazine, or a hydrate thereof, is carried out in a suitable solvent at a suitable temperature, generally an elevated

temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable solvents include pyridine and ethanol. Suitable reaction temperatures include those in the range of 60 °C to 220 °C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the product isolated by filtration, and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, hydrazine hydrate is added to a stirred solution of the compound of formula (IX) in pyridine. The reaction mixture is stirred at reflux for 6 hours and cooled. The crude product is isolated by filtration and dried. The crude product may be used without purification.

Compounds of formula (VIII) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formula (IX) may be prepared by reaction of a compound of formula (X),



(X)

wherein,

R^2, R^3 and R^4 are as defined in relation to formula (I), with a mixture of phosphorus oxychloride and phosphorus pentachloride.

The reaction between the compound of formula (X) and a mixture of phosphorus oxychloride and phosphorus pentachloride is carried out at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. Suitable reaction temperatures include the reflux temperature of the mixture. Suitable reaction times are those in the range 1-48 hours. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, and added cautiously to iced water. The solution is then basified with

a suitable base such as sodium carbonate and the product isolated by filtration. The product is then washed and dried. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction product may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, the compound of formula (X) is added to a suspension of phosphorus oxychloride and phosphorus pentachloride. The suspension is stirred at reflux for 1 hour, cooled, and cautiously added to iced water. The solution is adjusted to pH 11 with sodium carbonate and the product isolated by filtration, washed with water, and dried to afford the desired compound of formula (IX). The crude product may be used without purification.

Compounds of formula (X) are either commercially available or are prepared by analogy with known conventional literature procedures, for example those disclosed in *Recl. Trav. Chim. Pays-Bas, 1974, 93, 233*, or in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 4th Edition, 1992, Wiley Interscience.*

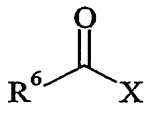
Compounds of formula (V) may be prepared by reaction of a compound of formula (VIII) with an aldehyde, R^6CHO, wherein R^6 is as defined in relation to formula (I).

The reaction between the compound of formula (VIII) and an aldehyde, R^6CHO, is carried out in a suitable solvent at a suitable temperature, generally an elevated temperature, providing a suitable rate of formation of the required product, over a suitable reaction time. A suitable aldehyde is benzaldehyde. A suitable solvent is butan-1-ol. It will be appreciated that in certain circumstances it may be advantageous to employ a suitable dehydrating agent, such as molecular sieves. Suitable reaction temperatures include the reflux temperature of the mixture. Suitable reaction times are those in the range 12-48 hours. The reaction products are isolated using conventional methods. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction product may, if desired, be purified by conventional methods, such as crystallisation, chromatography and trituration.

In a preferred aspect, a mixture of the compound of formula (VIII) and the aldehyde in butan-1-ol are heated at reflux, with stirring, for 12 to 24 hours, preferably 16 hours. The resulting reaction mixture is cooled to ambient temperature, and the resulting precipitate filtered, washed with a suitable solvent, such as butan-1-ol, and dried in a vacuum oven to afford the desired product of formula (V).

Compounds of formula (V) are believed to be novel and accordingly form a further aspect of the present invention.

Compounds of formula (VI) may be prepared by reaction of a compound of formula (VIII) with a compound of formula (XI),



(XI)

wherein R^6 is as defined in relation to formula (I), and X is a suitable leaving group.

Suitably X is chloro. It will also be appreciated that compounds of formula (XI) may include carboxylic acid anhydrides.

The reaction between the compounds of formulae (VIII) and (XI) is carried out in a suitable solvent under conventional amidation conditions, at a suitable temperature providing a suitable rate of formation of the required product, generally an elevated temperature, over a suitable reaction time. Suitable solvents include pyridine. Suitable reaction temperatures include those in the range of 60°C to 220°C and, as appropriate, the reflux temperature of the solvent. Suitable reaction times are those in the range 12 to 36 hours. If the compound of formula (VIII) is a weak nucleophile, then the reaction may be assisted by, for example, using temperatures at the upper end of this range, or by using a hindered base catalyst such as dimethylaminopyridine (DMAP). A hindered base is a base which does not act as a competing nucleophile. The reaction products are isolated using conventional methods. Typically, the reaction mixture is cooled, the residue acidified using a suitable acid and the products isolated by filtration. A suitable acid is a dilute mineral acid, for example dilute hydrochloric acid. Conventional methods of heating and cooling may be employed, for example thermostatically controlled oil baths and ice/salt baths respectively. The reaction products are purified by conventional

methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

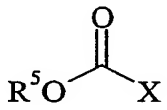
In a preferred aspect, the compound of formula (XI) is added to a solution of the compound of formula (VIII) in pyridine. The reaction mixture is stirred at reflux for 16 hours and allowed to cool. Following concentration of the reaction mixture, the residue is acidified with 2N HCl and the solid isolated by filtration. The crude product is purified by chromatography.

Certain compounds of formula (VI) are believed to be novel and accordingly form a further aspect of the present invention, with the proviso that the present invention does not encompass compounds of formula (VI) where R^2 and R^4 are H and R^3 is aryl.

Compounds of formula (VII) may be prepared by reaction of a compound of formula (I) wherein R^1 is halo and wherein R^2, R^3 and R^4 are as hereinbefore defined, with

a) n-butyllithium or sodium hydride and *tert*-butyllithium; followed by,

b) the addition of a compound of formula (XII),



(XII)

wherein R^5 is as defined in relation to formula (I) and X is a suitable leaving group. An example of a suitable leaving group, X, is chloro.

The reaction between the compounds of formulae (I) and (XII) is carried out in a suitable solvent, at a suitable temperature providing a suitable rate of formation of the required product over a suitable reaction time. Suitable solvents include tetrahydrofuran. Suitable reaction temperatures include those in the range of -90°C to -70°C. Suitable reaction times are those in the range 2 to 5 hours. The reaction products are isolated using conventional methods. Conventional methods of cooling may be employed, for example a liquid nitrogen/acetone bath. The reaction products are purified by conventional methods, such as crystallisation, chromatography and trituration. Crystalline product may be obtained by standard methods.

In a preferred aspect, the compound of formula (I) is dissolved in dry tetrahydrofuran and cooled to about -90 °C under an atmosphere of dry argon. N-butyllithium, suitably as a solution in a suitable solvent, such as hexanes, is added dropwise keeping the temperature below about -85 °C. The mixture is stirred at about -90 °C for a suitable period of time, such as from 5 to 30 minutes, preferably 10 minutes, and then *tert*-buyllithium is added dropwise, suitably as a solution in a suitable solvent, such as pentane, keeping the temperature below about -85 °C. The resulting mixture is stirred for a suitable period of time, such as from 5 to 30 minutes, preferably, 15 minutes, and the compound of formula (XII) is added dropwise in a suitable solvent, such as tetrahydrofuran. The resulting mixture is stirred for a suitable period of time, such as from 1 to 4 hours, preferably 2 hours, at about -90 °C, and then stirred for a further suitable period of time, such as from 15 to 45 minutes, preferably 30 minutes, at about -78 °C. The resulting mixture is allowed to warm to ambient temperature, and is subsequently treated with wet tetrahydrofuran, followed by water and ethyl acetate. The resulting residue is typically purified by chromatography on silica gel using a suitable solvent or mixture of solvents, such as dichloromethane/ether. The purified residue is then extracted with a suitable solvent, such as ether, to afford the desired compound of formula (VII).

Compounds of formulae (I), (V), (VI), (VIII) and (X) may exist as tautomers. The present invention encompasses all tautomeric forms of the compounds of (I), (V), (VI), (VIII) and (X).

As stated above, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are indicated to be useful as inhibitors of glycogen synthase kinase-3.

The invention therefore provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of GSK-3.

Accordingly, the present invention also provides a method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia,

amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The present invention further provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an inhibitor of glycogen synthase kinase-3, and especially for use in the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS

associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

In a further aspect of this invention, there is provided a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use as an active therapeutic substance.

Preferably, the compounds of formula (I), or pharmaceutically acceptable derivatives thereof, are administered as pharmaceutically acceptable compositions.

Accordingly, the invention also provides a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The active compounds are usually administered as the sole medicament agent but they may be administered in combination with other medicament agents as dictated by the severity and type of disease being treated.

The said combination comprises co-administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and an additional medicament agent or the sequential administration of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

Co-administration includes administration of a pharmaceutical composition which contains both a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent or the essentially simultaneous administration of separate pharmaceutical compositions of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and the additional medicament agent.

The compositions of the invention are preferably adapted for oral administration. However, they may be adapted for other modes of administration. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations, such as oral or sterile parenteral solutions or suspensions. In order to obtain consistency of administration it is preferred that a

composition of the invention is in the form of a unit dose. Preferably the composition are in unit dosage form. A unit dose will generally contain from 0.1 to 1000 mg of the active compound.

Generally an effective administered amount of a compound of the invention will depend on the relative efficacy of the compound chosen, the severity of the disorder being treated and the weight of the sufferer. However, active compounds will typically be administered once or more times a day for example 2, 3 or 4 times daily, with typical total daily doses in the range of from 0.1 to 800 mg/kg/day.

Suitable dose forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The formulations mentioned herein are carried out using standard methods such as those described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) or the above-mentioned publications.

Suitable methods for preparing and suitable unit dosages for the additional medicament agent, such as the antidiabetic agent mentioned herein include those methods and dosages described or referred to in the above-mentioned reference texts.

GSK-3 Assay

GSK-3 assays used to test the compounds of the invention include the following protocol which is based on the ability of the kinase to phosphorylate a biotinylated 26 mer peptide, Biot- KYRRAAVPPSPSLSRHSSPHQ(S)EDEEE, the sequence of which is derived from the phosphorylation site of glycogen synthase, where (S) is a pre-phosphorylated serine as in glycogen synthase *in vivo* and the three consensus sites for GSK-3 specific phosphorylation are underlined. The phosphorylated biotinylated peptide is then captured onto Streptavidin coated SPA beads (Amersham Technology), where the signal from the ^{33}P is amplified via the scintillant contained in the beads.

Using microtitre plates, GSK-3 was assayed in 50 mM MOPS buffer, pH 7.0, containing 5% glycerol, 0.01% Tween-20, 7.5 mM 2-mercaptoethanol, 10 mM magnesium acetate, 8 uM of the above peptide, and 10 uM [^{33}P]-ATP. After incubation at room temperature, the reaction was stopped by addition of 50 mM EDTA solution containing the Streptavidin coated SPA beads to give a final 0.2 mgs. Following centrifugation, the microtitre plates are counted in a Trilux 1450 microbeta liquid scintillation counter (Wallac). IC_{50} values are generated for each compound by fitting to a four parameter model.

The most potent compounds of the present invention show IC_{50} values in the range of 1 to 500 nM.

No adverse toxicological effects are expected for the compounds of the invention, when administered in accordance with the invention.

The following Descriptions and Examples illustrate the invention, but do not limit it in any way.

Synthetic Method A

Example 1

3-Bromo-5-phenyl-1H–pyrazolo[3,4-b]pyridine

Hydrobromic acid (0.5 mL, 48%) was added to 3-diazo-5-phenyl-3H-pyrazolo[3,4-b]pyridine (Description 1, 118 mg, 0.534 mmol) and the mixture heated with stirring at a bath temperature of 120° C for half an hour. After cooling to room temperature and diluting with water (5 mL) saturated sodium bicarbonate was added with stirring until effervescence ceased. The resulting solid was collected, washed with water and dried in vacuo to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 274/276 ($C_{12}H_8N_3Br$ requires $[M+H]^+$ at m/z 274/276). ^{1}H NMR δ (DMSO-d6): 7.36-7.58 (3H, overlapping m), 7.76-7.88 (2H, m), 8.27 (1H, m), 8.93 (1H, d) 14.12 (1H, br s).

The starting material for Example 1 may be prepared according to Description 1 below.

Description 1

3-Diazo-5-phenyl-3H-pyrazolo[3,4-b]pyridine

Concentrated sulphuric acid (3 mL) was added dropwise to a stirred suspension of 5-phenyl-1H-pyrazolo[3,4-b]pyridin-3-ylamine (0.953 g, 4.54 mmol) in chilled water (20 mL). Cooling was continued (ice/salt bath) and a solution of 40% aqueous sodium nitrite (1.5 mL) in water (1.5 mL) was then added dropwise keeping the temperature at 0° C. After half an hour stirring at bath temperature the mixture was basified with sodium carbonate and the resulting solid collected, washed with water and dried at room temperature under high vacuum to give the title compound as a solid.

MS (APCI+ve): $[(M-N_2+2H)+H]^+$ at m/z 196 ($C_{12}H_7N_5$ requires $[M+H]^+$ at m/z 222).

^{1}H NMR δ (DMSO-d6): 7.42-7.62 (3H, overlapping m), 7.76-7.87 (2H, m), 8.80 (1H, d), 8.98 (1H, d).

Synthetic Method B

Example 3

3-Chloro-5-phenyl-1H–pyrazolo[3,4-b]pyridine

Concentrated hydrochloric acid (5 mL) was added to 3-diazo-5-phenyl-3H-pyrazolo[3,4-b]pyridine (Description 1, 100 mg, 0.452 mmol) and the mixture stirred at room temperature overnight and then neutralized with saturated sodium bicarbonate solution. The resulting solid was collected, washed with water and dried *in vacuo* to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 230/232 ($C_{12}H_8N_3Cl$ requires $[M+H]^+$ at m/z 230/232).

^{1}H NMR δ (DMSO-d6): 7.36-7.60 (3H, overlapping m), 7.72-7.88 (2H, m), 8.39 (1H, m), 8.95 (1H, d) 14.00 (1H, br s).

Synthetic Method C

Example 4

(5-Phenyl-1H–pyrazolo[3,4-*b*]pyridin-3-yl)-(1H-pyrrol-2-yl)diazene

3-Diazo-5-phenyl-3H-pyrazolo[3,4-b]pyridine (Description 1, 100 mg, 0.452 mmol) was added with stirring to pyrrole (15 mL) at room temperature. After 2 days product was collected by filtration, washed with the minimum volume of dichloromethane and dried *in vacuo* to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 289 ($C_{16}H_{12}N_6$ requires $[M+H]^+$ at m/z 289).

^1H NMR δ (DMSO-d6): 6.39 (1H, m), 7.02 (1H, br m), 7.20 (1H, br m), 7.45 (1H, m), 7.55 (2H, t), 7.77 (2H, d), 8.82 (1H, d), 8.90 (1H, d), 12.22 (1H, br s), 14.08 (1H, br s)

Synthetic Method D

Example 5

5-(3-Fluorophenyl)-1H–pyrazolo[3,4-b]pyridine-3-carboxylic acid ethyl ester

3-Bromo-5-(3-fluorophenyl)-1H–pyrazolo[3,4-b]pyridine (425 mg, 1.45 mmol) was dissolved in dry tetrahydrofuran (30 mL) and cooled to -90° C under an atmosphere of argon. n-Butyllithium (1.6 molar solution in hexanes, 0.92 mL, 1.47 mmol) was added dropwise keeping the temperature below -85° C, the mixture was stirred at -90° C for 10 mins then t-butyllithium (1.7 molar solution in pentane, 1.75 mL, 2.97 mmol) was added dropwise keeping the temperature below -85° C. The mixture stirred at -90° C for 15 minutes then a solution of ethyl chloroformate (316 mg, 2.91 mmol) in tetrahydrofuran (2 mL) was added dropwise keeping the temperature below -85° C and the mixture stirred at -90° C for 2 hours then at -78° C for 30 minutes. The cooling bath was removed and the mixture allowed to warm to room temperature over 30 minutes. Wet tetrahydrofuran was added, followed by water and ethyl acetate. The organic layer was separated, washed with water and evaporated. The residue was chromatographed on silica gel (dichloromethane/ether) to give a semi solid which was extracted with ether to give 5-(3-fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridine-1,3-dicarboxylic acid diethyl ester as an oil after evaporation of solvent.

A mixture of 5-(3-fluorophenyl)-1H-pyrazolo[3,4-*b*]pyridine-1,3-dicarboxylic acid diethyl ester (44 mg, 0.123 mmol) and benzylamine (40 mg, 0.369 mmol) in ethanol (3 mL) was heated at reflux overnight. The solvent was evaporated and the residue chromatographed on silica gel (dichloromethane/ether) to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 286 ($C_{15}H_{12}FN_3O_2$ requires $[M+H]^+$ at m/z 286).

^1H NMR δ (DMSO-d6): 1.41 (3H, t), 4.45 (2H, q), 7.30 (1H, m), 7.60 (3H, m) 8.61 (1H, d), 8.97 (1H, d), 14.60 (1H, br s).

Synthetic Method E

Example 7

Benzyl-(5-phenyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-amine

A suspension of benzylidene-(5-phenyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-amine (150 mg, 0.50 mmol), sodium triacetoxyborohydride (540 mg, 2.54 mmol) and a few drops of glacial acetic acid in tetrahydrofuran (2 mL) was stirred at ambient temperature for 48 hours. Saturated sodium bicarbonate solution (5 mL) was added and the mixture extracted with ethyl acetate. The organic phases were combined, dried (anhydrous magnesium sulphate) and evaporated. The residue was purified by chromatography on silica gel with a gradient of dichloromethane - 10% acetone/dichloromethane to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 301 ($C_{19}H_{16}N_4$ requires $[M+H]^+$ at m/z 301).

^1H NMR δ (DMSO-d6): 4.49 (2H, d), 6.80 (1H, t), 7.20-7.49 (8H, m), 7.70 (2H, d), 8.50 (1H, d), 8.68 (1H, d), 12.05 (1H, s).

The starting material for Example 6 may be prepared according to Description 2 below.

Description 2

Benzylidene-(5-phenyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-amine

A solution of 5-phenyl-1*H*-pyrazalo[3,4-*b*]pyridin-3-ylamine (210 mg, 1.0 mmol) and benzaldehyde (0.11 mL, 1.1 mmol) was heated at reflux in butan-1-ol (6 mL) for 16 hours. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered, washed with butan-1-ol and dried in a vacuum oven to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 299 ($C_{19}H_{14}N_4$ requires $[M+H]^+$ at m/z 299).

^1H NMR δ (DMSO-d6): 7.42-7.59 (6H, m), 7.82 (2H, d), 8.10 (2H, dd), 8.66 (1H, d), 8.90 (1H, d), 9.31 (1H, s), 13.65 (1H, s)

Synthetic Method F

Example 8

Ethyl-(5-phenyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl)-amine

1.0M Lithium aluminium hydride in tetrahydrofuran (1 mL, 1.0 mmol) was added to a solution of N-[5-phenyl-1*H*-pyrazolo[3,4-b]pyridin-3-yl]acetamide (100 mg, 0.40 mmol) in 1,4-dioxan (5 mL). The reaction mixture was stirred at reflux for 2 hours, allowed to cool, a few drops of water added to decompose the excess lithium aluminium hydride and the solution concentrated. Purification by column chromatography (2% v/v methanol in dichloromethane) afforded the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 239 ($C_{14}H_{14}N_4$ requires $[M+H]^+$ at m/z 239).

^{1}H NMR δ (DMSO-d6): 12.0 (1H, s), 8.67 (1H, s), 8.42 (1H, s), 7.68 (2H, d), 7.49 (2H, t), 7.36 (1H, t), 6.18 (1H, t), 3.30 (2H, m), 1.24 (3H, t).

The starting material for Example 8 may be prepared according to Descriptions 3-5 below.

Description 3

2-Chloro-5-phenylnicotinonitrile

2-Oxo-5-phenyl-1,2-dihydropyridine-3-carbonitrile (2.50 g, 12.7 mmol) was added to a suspension of phosphorus oxychloride (1.5 mL) and phosphorus pentachloride (7.35 g) at room temperature. The suspension was then stirred at reflux for 1 hour. The reaction mixture was cooled to room temperature and added cautiously to iced water. The solution was then adjusted to pH 11 with sodium carbonate and the resulting white solid was filtered, washed with water, then dried *in vacuo* to afford the title compound as a solid.

^{1}H NMR δ (DMSO-d6): 8.8 (1H, d), 8.2 (1H, d), 7.6-7.5 (5H, m).

Description 4

5-Phenyl-1*H*-pyrazolo[3,4-b]pyridin-3-ylamine

Hydrazine hydrate (1.42 g, 28 mmol) was added to a stirred solution of 2-chloro-5-phenylnicotinonitrile (2.45 g, 11.4 mmol) in pyridine (25 mL). The reaction mixture was

stirred at reflux for 6 hours, cooled and the resulting solid was filtered and dried *in vacuo*, affording the title compound as a solid.

^{1}H NMR δ (DMSO-d6): 5.6 (2H, s), 7.4 (1H, d), 7.5 (2H, appt), 7.7 (2H, d), 8.4 (1H, d), 8.7 (1H, d), 12.0 (1H, br).

Description 5

***N*-(5-Phenyl-1H-pyrazolo[3,4-b]pyridin-3-yl)acetamide**

Acetic anhydride (0.41 mL, 4.35 mmol) was added to a solution of 5-phenyl-1H-pyrazolo[3,4-b]pyridin-3-ylamine (Description 4; 1.0 g, 4.76 mmol) in pyridine (5 mL). The reaction mixture was stirred at reflux for 16 hours, then allowed to cool. Most of the pyridine was removed under reduced pressure and 2N hydrochloric acid (15 mL) added. The resulting solids were filtered, washed with water and dried to afford the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 253 ($C_{14}H_{12}N_4O$ requires $[M+H]^+$ at m/z 253).

^{1}H NMR δ (DMSO-d6): 3.3 (3H, s), 7.4 (1H, d), 7.5 (2H, t), 7.7 (2H, d), 8.6 (1H, d), 8.8 (1H, d), 10.7 (1H, s), 13.3 (1H, s).

Synthetic Method G

Example 9

5-(3-Fluorophenyl)-1H–pyrazolo[3,4-b]pyridine-3-carboxylic acid n-butyl amide

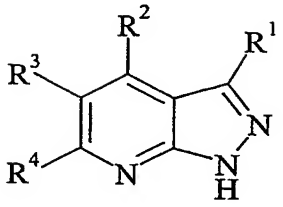
5-(3-Fluorophenyl)-1H–pyrazolo[3,4-b]pyridine-3-carboxylic acid ethyl ester (Example 5, 13 mg, 0.045 mmol) in n-butylamine (1 mL) was heated at reflux overnight. The solution was evaporated to dryness and the residue was triturated with ether to give the title compound as a solid.

MS (APCI+ve): $[M+H]^+$ at m/z 313 ($C_{17}H_{17}FN_4O$ requires $[M+H]^+$ at m/z 313).

^{1}H NMR δ (DMSO-d6): 0.90 (3H, t), 1.33 (2H, m), 1.56 (2H, m), 3.30 (2H, m) 7.26 (1H, m), 7.60 (3H, m), 8.54 (1H, t), 8.71 (1H, d), 8.93 (1H, d), 14.15 (1H, br s).

Further examples of the invention are illustrated in Table 1.

Table 1

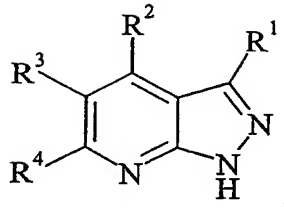


(I)

Example No.	Method	R^1	R^2	R^3	R^4	Calculated Mass	Observed [M+H]+ or [M-H]- or M-
1	A	Br	H	Ph	H	274.12	274/276
2	A	Br	H	3-F-Ph	H	292.11	292/294
3	B	Cl	H	Ph	H	229.669	230/232
4	C	N=N-2-pyrrolyl	H	Ph	H	288.313	289
5	D	CO2Et	H	3-F-Ph	H	285.277	286
6	E	NHCH2Ph	Ph	H	H	300.363	301
7	E	NHCH2Ph	H	Ph	H	300.363	301
8	F	NHEt	H	Ph	H	238.293	239
9	G	$CONHBu^n$	H	3-F-Ph	H	312.346	313

Claims

1. A compound of formula (I),



(I)

or a salt thereof, or a solvate thereof, wherein,

R^1 is halo, -N=N-heteroaryl, $-CO_2R^5$, $-NHCH_2R^6$; or $-CONR^7R^8$;

R^2 is H or aryl;

R^3 is H or aryl, wherein the aryl ring may be optionally substituted by one or more substituents, which may be the same or different, selected from halo;

R^4 is H;

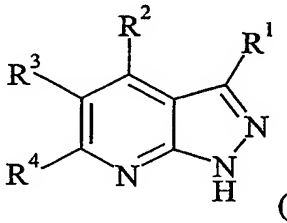
R^5 is alkyl; and

R^6 is H, alkyl, cycloalkyl, aryl or aralkyl; and

R^7 and R^8 are selected from H and alkyl;

with the proviso that when R^1 is halo, at least one of R^2 and/or R^3 is aryl.

2. A compounds of formula (I) as claimed in claim 1, of formula (IA),



(IA)

or a salt thereof, or a solvate thereof, wherein,

R^1 is bromo, chloro, -N=N-2-pyrrolyl, $-CO_2Et$, $-NHCH_2Ph$, –NHEt or $-CONHBu^n$;

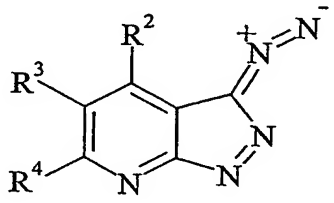
R^2 is H or phenyl;

R^3 is H, phenyl or 3-fluorophenyl; and

R^4 is H,

with the proviso that when R^1 is bromo or chloro, either R^2 is phenyl and/or R^3 is phenyl or 3-fluorophenyl.

3. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is halo and wherein R^2, R^3 and R^4 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I), with a compound of formula (III),

H—X

(III)

wherein X is halo, and thereafter, if required, carrying out one or more of the following optional steps:

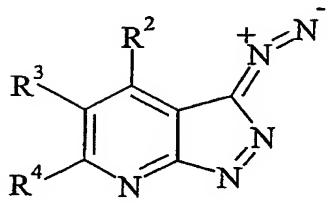
(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

4. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is –N=N-heteroaryl and wherein R^2, R^3 and R^4 are as hereinbefore defined

or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (II),



(II)

wherein R^2, R^3 and R^4 are as defined in relation to formula (I), with a compound of formula (IV),

Ar—H

(IV)

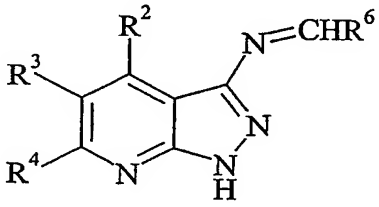
wherein Ar is heteroaryl, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

5. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is $-NHCH_2R^6$, and wherein R^2, R^3, R^4 and R^6 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (V),



(V)

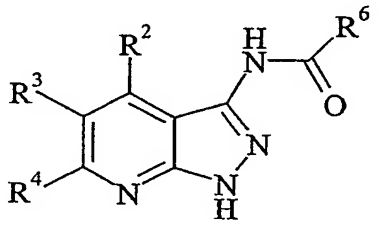
wherein R^2, R^3, R^4 and R^6 are as defined in relation to formula (I), with a reducing agent, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

6. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is $-NHCH_2R^6$, and wherein R^2, R^3, R^4 and R^6 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (VI),



(VI)

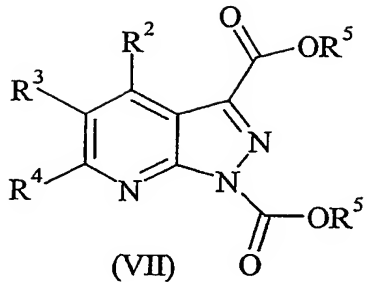
wherein R^2, R^3, R^4 and R^6 are as defined in relation to formula (I), with a reducing agent, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

7. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is $-CO_2R^5$, and wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (VII),



(VII)

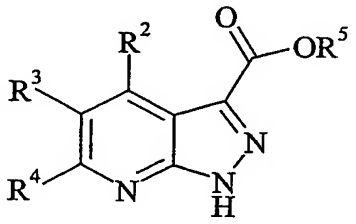
wherein R^2, R^3, R^4 and R^5 are as defined in relation to formula (I), with a nucleophile, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

8. A process for the preparation of a compound of formula (I), as claimed in claim 1, where R^1 is -$CONR^7R^8$, and wherein R^2, R^3, R^4, R^7 and R^8 are as hereinbefore defined or a salt thereof and/or a solvate thereof, which process comprises reacting a compound of formula (I) where R^1 is $-CO_2R^5$,



(I)

wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined, with an amine, NHR^7R^8, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing an appropriate derivative of the compound so formed.

9. A compound of formula (I), as claimed in claim 1, for use as an inhibitor of GSK-3.

10. A method for the treatment of conditions associated with a need for inhibition of GSK-3 such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency, which method comprises the administration of a pharmaceutically effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

11. Use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment of conditions associated with a need for the inhibition of GSK-3, such as diabetes, conditions associated with diabetes, chronic neurodegenerative conditions including dementias such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, Pick's disease, corticobasal degeneration, frontotemporal dementia, Huntingdon's disease, AIDS associated dementia, amyotrophic lateral sclerosis, multiple sclerosis and neurotraumatic diseases such as acute stroke, mood disorders such as schizophrenia and bipolar disorders, promotion of functional recovery post stroke, cerebral bleeding (for example, due to solitary cerebral amyloid angiopathy), hair loss, obesity, atherosclerotic cardiovascular disease, hypertension, polycystic ovary syndrome, syndrome X, ischaemia, traumatic brain injury, cancer, leukopenia, Down's syndrome, Lewy body disease, inflammation, and immunodeficiency.

12. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/13261

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P25/00 A61P9/00
//(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUCZYNSKI, LEONARD ET AL: "Biologically active pyrazolo'3,4-b!pyridine derivatives" retrieved from STN Database accession no. 93:239428 XP002234030 abstract and RN = 72583-78-9 & PL 106 896 P (POL.) 31 January 1980 (1980-01-31) ---	1,11
A	WO 95 34563 A (PFIZER) 21 December 1995 (1995-12-21) claims 1,12 ---	1,11
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 2003	21/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/13261

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 24694 A (SMITHKLINE BEECHAM) 28 March 2002 (2002-03-28) cited in the application claims 1,14	1,11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/13261

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/13261

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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